

LETTERS TO THE EDITOR

Renal and urological tract malformations caused by a 22q11 deletion

Deletions in the chromosomal region 22q11 cause a variable spectrum of congenital malformations recognised as either velocardiofacial syndrome (VCFS, Shprintzen syndrome) or DiGeorge syndrome. Typically these defects involve the heart (conotruncus and aortic arch), palate, thymus, parathyroid glands, and mesenchymal structures of the face. In addition, a large number of associated features have been reported.^{1,2}

Among the 39 patients with a 22q11 deletion followed at our centre, four have a well documented congenital nephrourological malformation. The first patient has bilateral obstructive megaureter discovered after he presented with acute pyelonephritis at the age of 1 month. The second patient has unilateral renal agenesis, which was detected during a cardiac catheterisation. The third patient had a right multicystic kidney, presenting as an abdominal mass and surgically removed at the age of 6 weeks. In the fourth patient, unilateral renal agenesis was detected during routine abdominal ultrasound in the neonatal period. Interestingly, in two patients, the urological malformation was discovered during routine screening. In our series, as not all patients with VCFS have so far been systematically screened for the presence of a nephrourological malformation, the incidence of urological malformations is probably higher than 10%.

Nephrourological malformations have been reported before in DiGeorge syndrome and VCFS and include renal agenesis,^{2,3} multicystic kidney dysplasia,^{4,5} vesicoureteral reflux,¹ and ectopic kidney.⁶ Also, hydrourter and hydronephrosis have been described in several patients with DiGeorge syndrome, but the data available do not allow the distinction between vesicoureteral reflux, obstructive megaureter, or pelviureteral junction obstruction.^{2,7} The frequent occurrence of nephrourological malformations in these syndromes strongly suggests that this is not coincidental, but rather a variable manifestation of the underlying genetic defect.

In the evaluation of children with a del(22q11), nephrourological investigation should therefore be mandatory. In the absence of overt disease, renal ultrasound would be the preferred method. Many patients with a 22q11 deletion have a congenital heart defect, and will undergo cardiac catheterisation. During this procedure, contrast medium is injected into the circulation and, therefore, renography and pyelography can easily be performed simultaneously. As shown by the second patient in this series, this can lead to the detection of a nephrouropathy.

These different urological malformations found in association with a 22q11 deletion can be regarded as the variable expression of the same embryological defect, that is, an abnormal development of the lower or upper

ureteral bud.^{8,9} The wide spectrum of urological malformations encountered within a single pedigree of branchio-oto-renal syndrome further illustrates that these urological malformations are pathogenetically related and can be caused by the same genetic defect.¹⁰

It is generally thought that the critical gene(s) in 22q11 must have a role in cranial neural crest migration or differentiation in the third and fourth pharyngeal pouches. However, the defects affect many other tissues. The present observation suggests that one or more gene(s) in 22q11 also have a role in ureter bud development. This is not unprecedented, since the Ret proto-oncogene has a critical role in both neural crest and ureter bud development. In mice, this gene is expressed in both the nervous system and in the ureter bud, and a homozygous disruption of the Ret gene in mice leads to renal dysplasia or agenesis and enteric aganglionosis.¹¹ Several genes have already been isolated from the critical deletion region on 22q11, and most of them show widespread expression, including in the kidney. However, it appears that gene expression in the metanephric mesenchyme or kidney alone probably cannot explain the spectrum of kidney malformations observed in 22q11 deletions. Rather, based upon the presented clinical evidence, candidate genes for DiGeorge or Shprintzen syndrome are therefore expected to show embryonic expression in the ureter bud.

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Unstable mutation in incontinentia pigmenti?

I note with interest the report by Kirchman *et al*¹ of possible gonadal mosaicism for incontinentia pigmenti (IP) in a healthy male. The authors report two paternal half sisters who manifest incontinentia pigmenti, and in whom the paternal X is preferentially inactivated. The authors' arguments and conclusions are, however, predicated on the assumption that the relevant mutation (that is, that resulting in IP) is stable. A number of observations in IP, however, have led to the hypothesis, first suggested by Traupe and Vehrung² that IP may be associated with an unstable mutation.

(1) Two reports exist of mother-son transmission of IP.^{3,4} This observation is inconsistent with the half chromatid mutation model⁵ put forward to explain the occurrence of IP in males who are cytogenetically normal (the majority of males with IP are cytogenetically normal, contrary to the authors' assertion that most have been found to have a 47,XXY karyotype^{2,6}).

(2) Mosaic phenotypic expression of skin abnormalities in females with IP follows Blaschko's lines and is thought to reflect the existence of two functionally distinct populations of cells as a result of (random) X inactivation. In cytogenetically normal males with IP, however, skin manifestations are also expressed mosaically.^{2-4,7} While this may be expected in sporadic (new mutation) males, and those with a 47,XXY karyotype, this would not be expected in the two cases of mother-son transmission, where the affected males are described as having features similar to females with IP. It might have been expected that males inheriting a maternal mutation might have diffuse disease affecting their entire skin. It might also have been expected that the occasional male with IP, who has a de novo mutation, might have diffuse involvement of skin in a segmental distribution, rather than the patchy distribution that is always seen.

(3) In his review of IP, Carney⁸ found a statistically significant tendency for daughters inheriting IP to have more severe manifestations than their mother, an indication of possible anticipation in IP.

If IP were found to be associated with an unstable mutation (?triplet repeat), this might explain not only the points already mentioned but also the case reported by Kirchman *et al*,¹ interpreted as gonadal mosaicism. In this case, the father might have a premutation which expanded on transmission to his daughters; this would be analogous to the normal transmitting male in fragile X.⁹ In addition, a recent report of three families with new mutations in IP, all originating in a male progenitor, would also be consistent with the NTM hypothesis, although a high rate of new mutations is to be expected in X linked conditions with reduced male fitness (for example, Duchenne muscular dystrophy¹⁰). The question of an unstable mutation in IP will only be resolved with the cloning of the gene and elucidation of causative mutations. A careful search for triplet expansions in Xq28

in families with IP may, however, be fruitful in the search for the gene.

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BOOK REVIEWS

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The A-Z Reference Book of Syndromes and Inherited Disorders. 2nd ed. Patricia Gilbert. (Pp 378; £15.99 pb.) London: Chapman & Hall. 1995. ISBN 0-412-64120-8.

The diagnosis of a rare condition in a child understandably raises many questions for that child's parents and relatives. Such queries are usually posed to the paediatrician or GP caring for the child. However, there are a wide range of health professionals involved in the care of the child who need information about a condition, both for themselves, and to answer the questions inevitably also posed to them. The problems of "how did it happen?", "can you treat it?", "will it happen again?", and many more are well addressed in this reference book.

Dr Gilbert has produced an expanded second edition of her book, designed to inform

health professionals and families after a syndrome diagnosis has been made. It has been specifically written in non-technical language, aimed at a general readership, who may not have a broad medical knowledge. Twenty new syndromes have been included at the request of readers, giving a total of 90 conditions, the majority of which are genetic. This is assisted by a clear appendix containing a good review of basic genetics by Peter Farndon. A useful glossary is also included. There is an alphabetical listing of each syndrome, with 1000 words or more per entry describing its incidence, history, causation, characteristics, management, and future developments. The descriptions show that Dr Gilbert has had extensive first hand experience in the care and management of children with rare disorders. The inclusion of the addresses of support group associations, Contact-A-Family, and the UK clinical genetics centres also shows her understanding of parents' needs. The language used for the most part is clear and simple to understand.

No such book could aim to cover all the rare syndromes. The author states that she can only cover a small number of syndromes. Her book is in fact an A-W of syndromes, although she could have made it an A-Z by including Zellweger's syndrome! There are also a few minor problems, such as the absence of any discussion of renal biopsy in Alport's syndrome, the omission of epilepsy as a complication of neurofibromatosis, and a rather unclear distinction between Finnish nephrotic syndrome and the many other causes of nephrotic syndrome. There is also no reference to the finding of an expanded triplet repeat causing fragile X syndrome, explaining the unusual inheritance. The index contains a list of signs and symptoms found in different syndromes, similar to that seen in Gorlin's *Syndromes of the Head and Neck*, ostensibly as an aid to diagnosis. In fact, this volume is better used as a reference once a diagnosis has already been made. The lack of photographs also makes this volume more suited to the role of a lay reference work, rather than a diagnostic aid.

Overall, this is an excellent reference book for a wide range of health and educational professionals. It provides clear clinical information, and can give a quick snapshot of a condition for many people involved in the care of children with rare disorders.

ANDREW GREEN

Maternal Genetic Disease. Edited by N B Isada, A Drugan, M P Johnson, M I Evans. (Pp 272; £65.95.) Stamford, Connecticut: Appleton and Lange. 1994. ISBN 0-8385-6164-0.

People who advise pregnant women need to keep up with developments in genetics. Parents always want to know the risks of passing a condition to their children and whether anything can be done to reduce these. Often the first person they ask is their obstetrician or midwife. This book, edited by a distinguished team from the United States and Israel, aims to provide the information required. It has some good features but these are outweighed by many faults.

The book opens with six chapters on general aspects of genetic diseases, including specifically preconception counselling, chromosomal problems, and mental retardation.

These deal with these problems in a similar way to most textbooks of genetics, albeit very briefly and with some important omissions. The book then changes character, and in the remaining 12 chapters a range of authors each tackle the genetic aspects of a specific maternal pregnancy problem, including the main medical problems that occur in pregnancy, renal, cardiac, haematological, neurological, and psychiatric disease, etc. This is a nice idea since, for generalists caring for pregnant women, these multifactorial conditions are much more common than the single gene defects on which most traditional genetic texts concentrate, and some chapters are very successful. However, for some diseases, once it has been stated that the inheritance is multifactorial, and the empirical recurrence risk given, there is little more to say. Unfortunately, this has not deterred contributors from padding out their chapters with platitudes, irrelevances, and repetitions, and the whole book cries out for stronger editing. The arrangement also leads to oddities. For example, cystic fibrosis (CF) appears only in chapters on anaesthesia and gastrointestinal disorders. The reason for the former appears to be that having written about malignant hyperpyrexia and succinylcholine sensitivity, the author needed a couple more pages to make a full chapter. The description of CF in the gastrointestinal chapter is concerned almost entirely with the important but rare problem of pregnancy in an affected woman. It is a quite inadequate guide to the day to day problems surrounding CF counselling and prenatal diagnosis for normal women with or without a family history.

There are many other omissions and imbalances. Some are serious and others simply rather strange. For example, myotonic dystrophy gets only five lines in one of the introductory chapters while multiple sclerosis gets 10 pages later on. It is unacceptable for a large genetics text in 1996 to omit any explanation of the whole area of triplet repeat sequences and genomic imprinting. Less serious, but still curious given the relative weight allocated to common multifactorial diseases, is the omission from a three page description of pre-eclampsia of any mention of the familial pattern of this disease. Readers will not learn that many experts even believe, albeit wrongly in my view, that this fascinating and common condition might be inherited in simple mendelian fashion, and that a number of groups are already doing gene linkage studies. They should be told.

This book bears all the hallmarks of being dashed off by busy authors and editors with more important calls on their time. I cannot recommend it.

J G THORNTON

The Molecular Biology and Pathology of Elastic Tissues. Ciba Foundation Symposium 192. (Pp 361; £49.95.) London: Wiley. 1995. ISBN 0-471-95718-6.

This book contains the published proceedings of an excellent Ciba Symposium on the molecular biology and pathology of elastic tissues held in Kenya in 1994. As one expects of Ciba Symposium proceedings, the book is beautifully produced and very portable. Furthermore, it has been published within less than 12 months.

North American dominance in the field is very evident with 72% of the chapters and a